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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,381	ZOGHBI ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21-39 and 47-55* is/are pending in the application.

4a) Of the above claim(s) *1-19,21-39,47 and 49-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3-13-03 & 1-20-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group X, claims 48 and 55, is acknowledged. The traversal is on the ground(s) that although the claimed subject matter is classified in different classes, the inventions are not independent such that it would not be an undue burden to search and examine all of the pending claims at the same time. This is not found persuasive because it does not set forth any reasoning as to why such a conclusion can be reached. The host of fusion proteins encompassed by the claims is innumerable and the search for all types of fusion proteins encompassed by the claims would be undue on the examiner. In addition, each fusion protein would have different issues under written description and enablement.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-19, 21-39, 47 and 49-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 1-20-04.

Upon further consideration, the species election of an atonal protein has been withdrawn.

Claims 48 and 55 are under consideration in the instant office action as they relate to nucleic acid sequences encoding a fusion protein comprising an "atonal-associated protein".

Priority

Nucleic acids encoding a fusion protein comprising an atonal-associated amino acid sequence has priority to 1-19-00, the filing date of provisional application 60/176993, but not 6-1-99, the filing date of provisional 60/137,060. '060 did not teach any fusion protein comprising an "atonal-associated protein" or a nucleic acid sequences encoding such a fusion protein.

The priority data in the bibliographic data sheet incorrectly claims priority to 60/147060 instead of 60/137060. A corrected filing receipt will be required.

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in PCT/US00/15410 on 6-1-00. It is noted, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b).

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37

CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequences on pg 33, line 21, and 51, line 14, do not have a SEQ ID NO.** If the sequence is already part of the sequence listing, simply amend the paragraph on pg 33 to include the proper SEQ ID NO. If the sequence on pg 33 is not listed in the originally filed sequence listing, a new sequence listing is necessary. Applicants must then file a new "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment and provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Applicant is requested to return a copy of the attached Notice to Comply with the reply. Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 48 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not adequately describe any nucleic acid sequence encoding a fusion protein comprising an atonal associated protein and a desired protein as broadly claimed. For written description purposes, the phrase "atonal associated protein" encompasses any known atonal protein such as math-1, 2, 3, 4, or 5, etc., any unknown atonal proteins, and those proteins that may be "associated" with any atonal protein in any signal transduction pathway or other developmental pathway, and the phrase "desired protein" has no boundaries. Thus, each component of the fusion protein is innumerable. Combining the two components into one fusion protein has countless possibilities.

The specification describes making a transgenic mouse using a nucleic acid construct with a deletion of the coding region of math1, wherein a lacZ gene is operably linked to the math1 promoter. The nucleic acid sequence in this section of the specification does not correlate to the claims because the nucleic acid does not encode a fusion protein or any part of an "atonal-associated amino acid sequence".

The specification states bacterial toxins can be used as delivery vehicles, such as Exotoxin A, cholera toxin and Ricin toxin (pg 72, line 17-19) but does not suggest making a fusion protein comprising an atonal protein and a bacterial protein; therefore, this section does not describe the claimed invention.

The specification contemplates combining an 11 amino acid "protein transduction domain" of HIV tat protein with atonal protein to make a fusion protein to allow a rapid dispersal into the nucleus of all cells of the body (pg 108, Example 22). This is the only

fusion protein described in the specification or that can be envisioned from the teachings in the specification.

An adequate written description of a nucleic acid sequence encoding a fusion protein requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the structure and function of the fusion protein and the nucleic acid sequence itself. Reference simply to any atonal fusion protein, especially any "atonal-associated protein" fusion protein, is not adequate written description of the fusion protein, and therefore, is not adequate written description of the nucleic acid sequence. Disclosure of no more than the desire to fuse an atonal protein with any other protein, as in the instant case, is simply a wish to know the structure or function of any such fusion protein. Naming a fusion protein generically known to be possible, in the absence of knowledge as to the structure and function of that fusion protein, is not a description of that material. The specification does not teach any non-atonal proteins that are "associated" with atonal proteins or how to make or use fusion proteins from non-atonal proteins. Combining an 11 amino acid "protein transduction domain" of HIV tat protein with atonal protein to make a fusion protein to allow a rapid dispersal into the nucleus of all cells of the body is a species amongst countless other species and does not represent the genus claimed. Thus, claiming all nucleic acids that encoding an atonal fusion protein without defining the structure or function of such a fusion protein is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has

arrived (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

The specification does not adequately describe any nucleic acid sequence encoding an atonal protein that provides a therapeutic effect; therefore, the specification does not adequately describe any nucleic acid sequence encoding an atonal fusion protein that provides a therapeutic effect. Therefore, the phrase "therapeutically effect amount of atonal-associated nucleic acid sequence" in claim 55 is not adequately described. The specification does not describe how to use any atonal protein to obtain a therapeutic effect. The specification describes the expression patterns and possible roles for some atonal proteins (pg 92-96, Example 13); however, the specification states the function of atonal proteins is yet to be analyzed (sentence bridging pg 95-96). The specification and the art at the time of filing did not describe the "amount" of any atonal protein or DNA encoding any atonal protein that was therapeutic. The specification describes adenoviral and retroviral vectors encoding atonal proteins and expressing atonal proteins in cells (pg 96-108, Examples 14-21); however, the specification does not teach the amount of protein expression that was therapeutic or obtaining any "therapeutic effect" in any cell. Since it was unknown how to use any atonal protein to obtain a therapeutic effect, it was unknown how to use a fusion protein comprising an atonal protein to obtain a therapeutic effect, and therefore, how to use a nucleic acid sequence encoding said fusion protein to obtain a therapeutic effect.

The specification describes using a fusion protein comprising an atonal protein and an HIV tat protein transduction domain to improve transduction. However, without

knowing how to target the fusion protein or the nucleic acid encoding the fusion protein to proper cells, the cells to target or the amount of atonal protein required to obtain a therapeutic effect, improving transduction is a moot point. Expressing atonal fusion protein in every cell does not have a disclosed use and may in fact negate any therapeutic effect. Atonal proteins are developmental proteins; overexpression of developmental proteins in every cell could negatively effect major underlying pathways and negate any possible therapeutic effect. The specification especially did not describe how to obtain a therapeutic effect *in vivo* using a nucleic acid encoding an atonal fusion protein.

While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pg 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg 198, col. 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (pg 53, 1st ¶). Deonarain reviews new techniques under experimentation in the art that show promise but states that such techniques are even

less efficient than viral gene delivery (see pg 65, 1st ¶ under Conclusion). Verma (Sept. 1997, Nature, Vol. 389, pg 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (pg 240, sentence bridging col. 2 and 3). Crystal (1995, Science, Vol. 270, pg 404-410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (pg 409).

The specification does not teach how to target DNA to any desired cells *in vivo*, the amount of atonal protein expression required to obtain a therapeutic effect *in vivo*, the specific combination of promoter and vector required to obtain "therapeutic effective amounts" of protein expression *in vivo* or the therapeutic effect that would occur *in vivo* using gene therapy. The specification teaches adenoviral and retroviral vectors encoding atonal proteins and transfecting cells *in vitro* (pg 96-108, Examples 14-21). Such teachings are not adequate for one of skill to overcome the unpredictability in the art to determine how to use a nucleic acid sequence encoding an atonal fusion protein to obtain a therapeutic effect as claimed.

The specification does not teach any "fragments" of atonal proteins that have a function that is of interest. The specification does not teach any assays for one of skill to determine whether an atonal protein fragment has a function of interest. Therefore,

the specification does not adequately describe any "fragments thereof" as claimed (claim 48).

2. Claims 48 and 55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence encoding a fusion protein, said fusion protein comprising an atonal protein operably linked to a protein transduction domain of HIV tat protein, does not reasonably provide enablement for any fusion protein as broadly claimed or any pharmaceutical composition that "results in delivery of a therapeutically effective amount of *atonal*-associated nucleic acid sequence into a cell". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 48 is drawn to a nucleic acid sequence encoding a fusion protein comprising an atonal associated protein and a desired protein. For enablement purposes, the phrase "atonal associated protein" encompasses any known atonal protein such as math-1, 2, 3, 4, or 5, etc., any unknown atonal proteins, and those proteins that may be "associated" with any atonal protein in any signal transduction pathway or other developmental pathway, and the phrase "desired protein" has no boundaries. Thus, each component of the fusion protein is innumerable. Combining the two components into one fusion protein has countless possibilities.

The specification describes making a transgenic mouse using a nucleic acid construct with a deletion of the coding region of math1, wherein a lacZ gene is operably linked to the math1 promoter. The nucleic acid sequence in this section of the

specification does not correlate to the claims because it does not encode a fusion protein or any part of an "atonal-associated amino acid sequence".

The specification states bacterial toxins can be used as delivery vehicles, such as Exotoxin A, cholera toxin and Ricin toxin (pg 72, line 17-19) but does not suggest making a fusion protein comprising an atonal protein and a bacterial protein; therefore, this section does not correlate to the claims.

The specification explicitly contemplates combining an 11 amino acid "protein transduction domain" of HIV tat protein with atonal protein to make a fusion protein to allow a rapid dispersal into the nucleus of all cells of the body (pg 108, Example 22). The specification does not teach how to make or use any other fusion protein. No other atonal fusion proteins are implicit in the teachings of the specification. The specification does not teach any fusion proteins comprising non-atonal proteins as encompassed by "atonal-associated proteins." Teachings regarding the function of other possible atonal fusion proteins are especially deficient and could not have been envisioned by one of skill in the art at the time of filing. It would have required one of skill in the art undue experimentation to determine the structure or function of any other atonal fusion proteins other than the one described in Example 22. Therefore, the specification does not enable any nucleic acid sequence encoding any "atonal-associated protein" fusion protein as broadly claimed.

The phrase "therapeutically effect amount of atonal-associated nucleic acid sequence" in claim 55 is not enabled. The specification does not teach how to use any atonal protein to obtain a therapeutic effect. The specification describes the expression

patterns and possible roles for some atonal proteins (pg 92-96, Example 13). The specification states the function of atonal proteins is yet to be analyzed (sentence bridging pg 95-96). The specification and the art at the time of filing did not describe the "amount" of any atonal protein or DNA encoding any atonal protein that was therapeutic. Different atonal proteins have different functions, none of which, by themselves, had been used to obtain a therapeutic effect. The specification describes adenoviral and retroviral vectors encoding atonal proteins and expressing atonal proteins in cells (pg 96-108, Examples 14-21); however, the specification does not teach the amount of protein expression that was therapeutic or obtaining any "therapeutic effect" in any cell. Since it was unknown how to use any atonal protein to obtain a therapeutic effect, it was unknown how to use a fusion protein comprising an atonal protein to obtain a therapeutic effect, and therefore, how to use a nucleic acid sequence encoding said fusion protein to obtain a therapeutic effect.

The specification describes using a fusion protein comprising an atonal protein and an HIV tat protein transduction domain to improve transduction. However, without knowing how to target the fusion protein or the nucleic acid encoding the fusion protein to proper cells, the cells to target or the amount of atonal protein required to obtain a therapeutic effect, improving transduction is a moot point. Expressing atonal fusion protein in every cell does not have a disclosed use and may in fact negate any therapeutic effect. Atonal proteins are developmental proteins; overexpression of developmental proteins in every cell could negatively effect major underlying pathways and negate any possible therapeutic effect. It would have required one of skill in the art

undue experimentation to determine how to use the protein to obtain a therapeutic effect, how to target cells of interest, and the function of an atonal protein in any cell as broadly claimed. As such, it would have required one of skill in the art undue experimentation to determine how to use a nucleic acid sequence encoding an atonal fusion protein to obtain a therapeutic effect, how to target cells of interest, and the function of an atonal protein in any cell as broadly claimed.

The specification especially did not teach how to obtain a therapeutic effect *in vivo* using a nucleic acid encoding an atonal protein.

While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pg 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg 198, col. 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (pg 53, 1st ¶). Deonarain reviews new techniques under experimentation in the art that show promise but states that such techniques are even less efficient than viral gene delivery (see pg 65, 1st ¶ under Conclusion). Verma (Sept.

1997, Nature, Vol. 389, pg 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (pg 240, sentence bridging col. 2 and 3). Crystal (1995, Science, Vol. 270, pg 404-410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (pg 409).

The specification does not teach how to target DNA to any desired cells *in vivo*, the amount of atonal protein expression required to obtain a therapeutic effect *in vivo*, the specific combination of promoter and vector required to obtain "therapeutic effective amounts" of protein expression *in vivo* or the therapeutic effect that would occur *in vivo* using gene therapy. The specification teaches adenoviral and retroviral vectors encoding atonal proteins and transfecting cells *in vitro* (pg 96-108, Examples 14-21). It would have required one of skill in the art undue experimentation to determine how to determine the specific combination of parameters required to overcome the art established unpredictability of gene therapy and obtain a therapeutic effect using a nucleic acid sequence encoding an atonal fusion protein as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 48 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "atonal-associated protein" is indefinite (claims 48 and 55). The phrase "atonal-associated" is defined as "any nucleic acid sequence or amino acid sequence which is the *Drosophilae atonal* nucleic acid sequence or amino acid sequence, or is any sequence which is homologous to or has significant sequence similarity to said nucleic acid or amino acid sequence, respectively." Significant sequence similarity means "greater than 25% and can occur in any region of another sequence." (pg 23, lines 9-15). Applicants' definition is unclear because proteins having 25% homology to a Drosophilae atonal protein would not share essential structures or functions. It is unclear how any protein sharing 25% homology with any drosophilae atonal protein could reasonably be considered "associated" with an atonal protein. It is unclear if some essential structure or function is also required to determine "atonal-associated" proteins. As such, it cannot be determined if the phrase is limited to:

i) mouse atonal homologues (math1, 2, etc.), human atonal homologues (hath), chicken atonal homologues (cath), xenopus atonal homologues (xath), etc.;

ii) math, hath, cath, xath, etc. and other "atonal" proteins that are in the "atonal" protein family but not called "atonal" proteins; or

iii) atonal proteins and proteins "associated" with atonal proteins, i.e. non-atonal proteins involved in the same signal transduction pathway, non-atonal proteins that bind to atonal proteins, non-atonal proteins that share similar structure (25% homologous),

non-atonal proteins that have 25% homology with an amino acid sequence of 10, 100, 1000, or 10,000 amino acids, or non-atonal proteins that share the same function.

The phrase "desired amino acid sequence" is indefinite (claim 48). The metes and bound of what applicants considered "desired" cannot be determined and are not readily apparent to one of skill in the art. It cannot be determined which amino acids one of skill would express an interest in fusing to an atonal protein.

The phrase "therapeutically effective amount of atonal-associated nucleic acid sequence" is unclear. Such an amount is not defined and may vary depending upon the protein. In fact, the therapeutic effect of any particular atonal protein is not clear; therefore, the amount of atonal protein expression required to be therapeutic cannot be determined, and the amount of "atonal-associated nucleic acid sequence" that is therapeutic cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 48 and 55 are rejected under 35 U.S.C. 102(a) as being anticipated by Schwarze (Science, Sept. 3, 1999, Vol. 285, pg 1569-1572).

Schwarze taught a nucleic acid sequence encoding β-gal operably linked to an HIV tat protein transduction domain (¶ bridging pg 1569-1570). β-gal is an "atonal associated protein" because it shares 100% homology with 3 amino acids out of a sequence of 10 amino acids of a Drosophilae atonal protein. This is greater than 25% homology, which is all that is required in applicants' definition of "atonal-associated proteins." In an alternative interpretation, β-gal is a "fragment thereof" because it shares 100% with 3 amino acids out of a sequence of 10 amino acids of a Drosophilae atonal protein (i.e. the 3 amino acids are a "fragment thereof"). The amount of nucleic acid taught by Schwarze is "a therapeutically effective amount of atonal-associated nucleic acid sequence" because the metes and bounds of such an amount are unclear (112/2nd), because the amount caused delivery of the protein to the nucleus of cells, which may be considered a "therapeutic effect," and because the amount is equivalent to an amount that does cause a therapeutic effect. Claim 55 merely requires delivery of a "therapeutically effective amount" and does not require obtaining a therapeutic effect.

5. Claims 48 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwab (J. Neurosci. Feb 15, 1998, OE (4) pg 1408-1418).

Schwab taught a nucleic acid sequence encoding an NEX fragment operably linked to a neomycin resistance gene (pg 1409, col. 1, 2nd ¶). NEX is an "atonal associated protein" because it was known to be a helix loop helix protein independently cloned as MATH2 (pg 1408, col. 2, line 4-9) and has greater than 25% homology with a Drosophilae atonal protein. The amount of nucleic acid taught by Schwab is "a therapeutically effective amount of atonal-associated nucleic acid sequence" because

the metes and bounds of such an amount are unclear (112/2nd) and because the amount caused the absence of gliosis (¶ bridging pg 1410-1411), which may be considered a "therapeutic effect," and because the amount is equivalent to an amount that does cause a therapeutic effect. Claim 55 merely requires delivery of a "therapeutically effective amount" and does not require obtaining a therapeutic effect.

6. Claims 48 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown (Development, 1998, Vol. 125, pg 4821-4833).

Brown taught a nucleic acid sequence encoding Math5 operably linked to a myc-epitope tag (pg 4823, col. 1, 1st ¶). Math5 has greater than 25% homology with a Drosophilae atonal protein. The amount of nucleic acid taught by Brown is "a therapeutically effective amount of atonal-associated nucleic acid sequence" because the metes and bounds of such an amount are unclear (112/2nd) and because the amount is equivalent to an amount that does cause a therapeutic effect. Claim 55 merely requires delivery of a "therapeutically effective amount" and does not require obtaining a therapeutic effect.

In an alternative interpretation, claim 55 is rejected because Brown taught administering GFP DNA in combination with Xath5, Math5 or Mash1 DNA. The amount of nucleic acid taught by Brown is "a therapeutically effective amount of atonal-associated nucleic acid sequence" because the metes and bounds of such an amount are unclear (112/2nd), because the amount caused an increase in bipolar cells (sentence bridging pg 4828-4829) and because the amount is equivalent to an amount

that does cause a therapeutic effect. Again, claim 55 merely requires delivery of a "therapeutically effective amount" and does not require obtaining a therapeutic effect.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 48 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown (Development, 1998, Vol. 125, pg 4821-4833) in view of Schwarze (Science, Sept. 3, 1999, Vol. 285, pg 1569-1572).

Brown taught administering GFP DNA in combination with Xath5, Math5 or Mash1 DNA. The amount of nucleic acid taught by Brown is "a therapeutically effective amount of atonal-associated nucleic acid sequence" because the metes and bounds of such an amount are unclear (112/2nd), because the amount caused an increase in bipolar cells (sentence bridging pg 4828-4829) and because the amount is equivalent to an amount that does cause a therapeutic effect. Claim 55 merely requires delivery of a "therapeutically effective amount" and does not require obtaining a therapeutic effect. Brown does not teach making a fusion protein encoding an atonal protein and an HIV tat protein transduction domain.

However, Schwarze taught a nucleic acid sequence encoding β-gal operably linked to an HIV tat protein transduction domain (¶ bridging pg 1569-1570). β-gal is an also "atonal associated protein" because it shares 100% with 3 amino acids out of a sequence of 10 amino acids of a Drosophilae atonal protein.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect cells with DNA encoding atonal proteins as taught by Brown and fusing an HIV tat protein transduction domain to the protein as taught by Schwarze. One of ordinary skill in the art at the time the invention was made would have been motivated to add the HIV tat protein transduction domain to the atonal proteins to dramatically enhance transduction potential in cultured cells (Schwarze, pg

1572, lines 1-4). Fifty proteins ranging in size from 15-120 kD were transduced in a wide variety of human and murine cell types using the HIV tat protein transduction domain (pg 1570, col. 2, lines 12-16).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

8. Claims 48 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akazawa (J. Biol. Chem., 1995, Vol. 270, No. 15, pg 8730-8738) in view of Schwartze (Science, Sept. 1999, Vol. 285, pg 1569-1572).

Akazawa taught transfecting eukaryotic cells with a vector encoding mouse atonal protein 1 (math1) (pg 8734, col. 2). Akazawa did not teach the vector encoded a fusion protein comprising math1.

However, Schwarze taught a nucleic acid sequence encoding β-gal operably linked to an HIV tat protein transduction domain (¶ bridging pg 1569-1570). β-gal is also an also "atonal associated protein" because it shares 100% with 3 amino acids out of a sequence of 10 amino acids of a Drosophilae atonal protein.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect cells with a vector encoding math1 as taught by Akazawa and fusing an HIV tat protein transduction domain as taught by Schwartze to the math1 protein. One of ordinary skill in the art at the time the invention was made would have been motivated to add the HIV tat protein transduction domain to the math1 protein to dramatically enhance transduction potential in cultured cells (Schwarze, pg 1572, lines 1-4). Fifty proteins ranging in size from 15-120 kD were transduced in a

wide variety of human and murine cell types using the HIV tat protein transduction domain (pg 1570, col. 2, lines 12-16).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

9. Claims 48 and 55 of this application conflict with claims 112 and 117 of Application No. 09/585,645. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 48 and 55 are provisionally rejected under the judicially created doctrine of double patenting over claims 112 and 117 of copending Application No. 09/585,645. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Claims 112 and 55 both require an atonal-associated nucleic acid sequence in a delivery vehicle that results in delivery of a therapeutically effective amount of atonal-associated nucleic acid sequence into a cell. Claims 117 is dependent upon claim 112 and requires the atonal protein is fused to a protein transduction domain. Claim 117 is a species of claim 48 and 55 in the instant application.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other

copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER